Sunscreens, Skin Photobiology, and Skin Cancer: The Need for UVA Protection and Evaluation of Efficacy

Francis P. Gasparro

Photobiology Laboratory, Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, Pennsylvania USA

Sunscreens are ultraviolet radiation (UVR)-absorbing chemicals that attenuate the amount and nature of UVR reaching viable cells in the skin. They are selected and tested for their ability to prevent erythema. No sunscreen prevents photodamage, as it has been demonstrated that suberythemal doses of UVR cause a variety of molecular changes (including DNA damage) in these cells. Furthermore, the spectrum of UVR reaching viable cells is altered by topically applied sunscreen. In this review, the basic aspects of sunscreens and skin photobiology are reviewed briefly. Although there can be no question concerning the efficacy of sunscreens for the prevention of erythema, questions remain because of the possible cumulative effects of chronic suberythemal doses and the increased exposure of skin cells to longer UVR wavelengths. The current major issue surrounding sunscreens involves their ability to protect skin cells against the effects of UVA radiation. These UVA effects may be direct damage (base oxidations) or effects on the skin immune system, yet there is no uniformly accepted method for the evaluation of UVA protection. This review is focused primarily on the latter topic covering action spectra that implicate the need for UVA protection. In addition, *in vivo* and *in vitro* methods proposed for the evaluation of candidate sunscreen formulations of UVA protective ability are reviewed. Finally, revisions in the terminology used to describe the protection afforded by sunscreens are suggested. It is proposed that SPF ("sun" protection factor) be renamed "sunburn" protection factor and that "critical wavelength" be designated "long wave index." *Key words*: critical wavelength, long wave index, sun protection factor, sunburn protection factor, ultraviolet radiation. — *Environ Health Perspect* 108(suppl 1):71–78 (2000).
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Sunscreens were originally developed to minimize erythema (*1,2*). However, for many years these products provided minimal skin protection and in fact were often referred to as suntan lotions. The concern about the long-term consequences of early childhood sunburn experiences and their apparent correlation with the development of cancer later in life led to the public education campaign promoting the frequent use of sunscreens in the 1980s. The comfort associated with the scientific basis of this message was correlated with the known photochemical effects of ultraviolet B (UVB) (cyclopyrimidine dimer formation), which led to the widespread acceptance of this message. The impact of this public health message was furthered by the newly appreciated effects of ozone depletion on the levels of UVB that might reach the surface of the earth (*3*). However, subsequent studies showed that these sunscreens were not preventing other effects in skin. Specifically, it was demonstrated in both animal and human studies that other non-erythemal effects were occurring as a result of the cumulative exposure to suberythemal amounts of solar radiation (*4*). These photoaging-type effects eventually were attributed to the UVA portion of UV radiation (UVR) being transmitted through the sunscreen-protected skin. More recently, the possible contribution of these transmitted wavelengths to the development of skin cancers has also become more fully appreciated.

The solar spectrum at the earth's surface is dramatically filtered by stratospheric ozone. The UV spectrum has been divided into three regions: UVA, 320–400 nm; UVB, 290–320 nm; and UVC, 200–290 nm (*5*). These definitions date back to early part of this century and were not biologically based. Rather, they represented convenient designations based on the transmission of common optical filters in use at that time. The UVA region has been further divided more recently. The range from 320 to 400 nm has been designated UVA-II because the molecular effects induced by these wavelengths are similar to UVB wavelengths (i.e., causing direct DNA damage; see next section).

UVA Effects in Skin

DNA Damage

The best-characterized effects of UVR exposure are those evident in DNA. Beukers and Berends (*6*) first described the photochemical linking of thymines after irradiating frozen aqueous solutions with UVC radiation. Their occurrence and repair several years later in DNA from *in vivo* irradiated cells were described by Setlow and Carrier (*7*). Pyrimidine dimer formation and repair in human skin were described by Sutherland et al. (*8*). Careful experiments since then have demonstrated a correlation between the action spectrum for DNA damage induction and sunburn (*9*). Because an action spectra defines the relationship between some property and the wavelengths of radiation used to induce the effect, it is the most informative and probably most important of all photobiologic phenomena. An action spectrum for the induction of erythema in human skin was originally reported early in this century (*10*).

Other Skin Chromophores

Although the primary chromophore of concern in the case of UVB and UVA-II exposure is DNA, protein components also absorb these wavelengths, yet little *in vitro* or *in vivo* photochemistry of these moieties has been reported. In addition, longer wavelength photons (UVA-I) may be absorbed by other endogenous molecules that can transfer excited-state energy to DNA, leading to photooxidation of selected bases [see next section; for an introduction to basic principles of photochemistry, see Kochevar (*11*)]. Other effects may be traced to clastogenic factors generated from other uncharacterized photoreactions [e.g., lipid oxidation; see Morliere et al. (*12*)]. In addition, it has been suggested that the UVA component of solar radiation may induce lipid peroxidation, which can subsequently stimulate the migration of important immune-mediating skin resident cells from the epidermis and thereby lead to skin immune suppression. Furthermore, Tyrrell and Pidoux (*13*) show that only 40% of cytotoxic effects from sunlight (290–434 nm) was due to the UVB component. The cited studies also highlight the limitations of laboratory sources. Although these studies are convenient and reproducible, they do not exactly replicate the sun; when studies using artificial sources are compared, it is important to verify their similarities (*14*). Often the same source may have been employed (e.g., FS-40 sunlamps), but in one case with UVC filtering and in the other without filtering (*15*). Another particularly good example of a comparative study was published recently (*16*). For a comprehensive

Address correspondence to F.P. Gasparro, Photobiology Laboratory, Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, 233 South 10th St. (Bldg 428), Philadelphia, PA 19107. Telephone: (215) 503-3327. Fax: (815) 371-0221. E-mail: francis.gasparro@mail.tju.edu or fotondoc@aol.com. Website: www.fotondoc.com

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review of the effects of UVR for the general scientific audience, see de Gruijl (*17*) and Diffey (*18*).

Appropriateness of Animal Models—Pitfalls and Remedies

To study the chronic effects of UVR exposure in skin, it has been necessary to employ animals. For the most part, mice have been accepted as a reasonable model for human skin response to UVR exposure. Chronic exposure of murine skin to UVR leads to the development of one type of skin cancer, squamous cell carcinoma (SCC) (*19*). In human skin, in addition to SCC, basal cell carcinoma (BCC) and malignant melanoma (MM) are commonly found and thought to be induced by chronic solar exposure (*20*). However, because there has been little success in development of convenient animal models for these malignancies, precise animal studies to explore dose and wavelength dependencies have not been performed. An opossum model has been used for the study of UVR induction of melanoma. Studies in this system suggest that portions of the UVA spectrum may play a significant role in the development of melanoma (*21,22*).

Mice commonly employed for skin photobiology studies have few melanocytes in the skin areas exposed to UVR. However, there are some interesting new models on the horizon. In an attempt to create a human skin model system for laboratory studies, Attilasoy et al. described the induction of melanocytic lesions in human foreskins transplanted to the backs of *scid* mice (*23*). One melanoma and several melanocytic lesions were found in the grafted skin. In the group of mice who received only UVB (3× per week for up to 12 months), 23% of the skin grafts developed solar lentigines in 5–10 months. When the UVB regimen was preceded by a single application of dimethylbenz[*a*]anthracene, the frequency increased to 38%. The sole melanoma was found in the latter group of mice. In these studies the UVR source employed emitted radiation primarily in the UVC and UVB regions. The amount of UVA in the source was small compared to that found in natural sunlight, thus these studies represent a single point in an action spectrum for the induction of melanocytic lesions (*24*).

Mintz and Silvers have described the development of melanoma in a transgenic murine model (Tyr-SV40E) with melanoma susceptibility (*25*). Different inbred lines are susceptible to different extents. In moderately susceptible mice, melanomas could be induced after four successive daily exposures to UVB radiation. Although it has been suggested that these mice could be used to determine an action spectrum for melanoma induction, more recent studies have examined nine different protocols for the induction of melanoma. The highest incidence of melanoma (five melanomas in 19 mice) was found using a protocol in which the mice were exposed to 0.38 J/cm^2 UVB/day for 5 days starting at 3 days of age (*26*).

Another transgenic mouse with melanocytes residing in many anatomical areas has been described recently (*27*). The epidermis of these transgenic mice, bearing a keratin 14 promoter-driven modified cDNA for stem cell factor (the ligand of the kit receptor, tyrosine kinase), have keratinocytes that continue to express stem cell factors beyond the neonatal period, resulting in the maintenance of a population of pigment-producing melanocytes in the skin throughout their lifetime. These mice develop postinflammatory hyperpigmentation in response to irritant and allergic contactants. Whether these could be a candidate animal model for the study of the action spectrum for the induction of MM remains to be determined. Others have suggested replacing animal studies with human skin equivalents (*28*). However, it remains to be determined how relevant such a system can be. Its utility may be limited to developing techniques for the eventual application to *in vivo* photochemistry.

Application of Murine Data to the Evaluation of Human Skin Cancer Risk

The carefully determined murine action spectrum for SCC has been mathematically adjusted to account for human skin parameters (*29*). It is from these data that we can infer with a high degree of confidence that screening UVB radiation may attenuate the development of SCC in human skin (*30*). Furthermore, although limited, there are actual human experimental data. Thompson et al. have shown that the regular use of a high potency sunscreen (sun protection factor [SPF]-17 containing both UVB and UVA absorbing ingredients) could prevent solar keratoses (*31*). These results imply the possibility that by preventing keratoses, skin cancers may be prevented as well.

Synergistic Effects of UVB and UVA

Possible interactions between UVB and UVA have not been extensively tested (not even indirectly), as primarily UVB-rich sources have been employed for laboratory studies. However, human skin is rarely exposed to isolated regions of the UV spectrum (*32*). Chung and Youn demonstrated that UVB increased the production of interleukin(IL)-1, whereas UVA suppressed it (*33*). UVA also suppressed the UVB induction of the cytokine. However, a more recent study using human volunteers demonstrated no correlation between UVA pre-exposure and the development of UVB-induced erythema (*34*).

Pigmentation Effects

Exposure of human skin also leads to darkening effects, the extent of which depends on individual skin type (*35*). Immediate pigment darkening (IPD), likely the result of photo-oxidation processes, can be observed with minutes of solar exposure (*36*). In contrast, delayed pigment darkening occurs over a somewhat longer time period. Although the former offers little if any skin protection against solar radiation, the latter effect is derived from the production of melanin as an adaptive, protective response against further UVR damage. In addition to different kinetics and protective effects, the action spectra for their induction may differ. The maximum wavelength for the induction of IPD is approximately 340 nm (*36*), whereas delayed pigmentation parallels the erythema action spectrum. In other studies, it has been shown that pigmentation effects are also accompanied by varying degrees of epidermal thickening (*37*), so that even individuals who develop little pigmentation as a result of sun exposure can develop some limited UVR tolerance. This is not meant to encourage UVR exposure in these individuals but rather to emphasize the complexities of the response of human skin to UVR.

Is Skin Pigmentation Protective?

The answer to this question is not a simple one. The significant differences in the incidences of all skin cancers in blacks versus Caucasians strongly suggest a protective effect from pigmentation (*38*). The tan acquired by overly exposed Caucasian skin also offers some protection from erythema (*39*). Whether this same level of pigmentation also protects skin from cancer has been the subject of some debate. In a recent report Lock-Andersen et al. measured constitutive and facultative skin pigmentation in Caucasians with BCC and cutaneous malignant melanoma (CMM) (*40*). Although they expected to find that constitutive skin pigmentation would be lower in these patients, they were surprised to find neither a statistical difference between patients and controls nor any difference between CMM and BCC patients. These observations suggest that factors other than pigmentation may be important in skin cancer etiology. Among these possible factors are reduced skin repair capacity in fair-skinned subjects and possibly the presence of a higher proportion of the less protective pheomelanin (rather than eumelanin). Regarding the former, D'Errico et al. quantified DNA repair capacity (DRC) in 49 patients with BCC and 68 cancer-free controls (*41*). A statistically significant age-related decline in DRC was observed in the control group but not the BCC group. When comparisons were made on the basis of age, it

was shown that young BCC cases (less than 40 years of age) repaired less than the controls but without statistical significance. Older BCC patients (more than 40 years of age) demonstrated enhanced DRC ($p < 0.0001$). In other kinds of internal cancers, it had been demonstrated that a mean DRC in the range of 65–95% of the general population is usually more frequent in the cancer cohorts. However, transient effects on DRC may be a confounding factor. Among these are recent exposures to UVR itself. The role of DRC in the potential evaluation or the development of skin cancer needs further study.

The answer to the title question for medium and darker skin types may be more complicated. For the most part it appears that outdoor workers become acclimated to sun exposure by a variety of mechanisms (*42*). In fact, most skin adapts to chronic (not necessarily excessive) sun exposure. Recent skin cancer statistics indicate that skin cancers of any kind were found in less than 15% of a screened population (*43*). Certainly many of the 85% without skin cancers may have avoided sun (at least in their adult years), yet many (most likely the vast majority) have probably spent considerable time in the sun during their lifetimes.

In recent years an entire industry has grown up around the concept of acquiring and/or maintaining tanned skin by exposure to artificial sources of UVA. There is limited data indicating any long-term ill outcome in terms of skin cancer, although there is evidence of significant actinic-type damage (*44*). Almost certainly excessive tanning will lead to photoaged skin in these frequent tanners. In addition an unknown percentage will have an increased incidence of skin cancers. However, it will not be a simple task to deconvolute the relative contributions of natural solar exposure and artificial tanning. However, actual data are not available at this time to determine whether the incidence of skin cancer in artificial tanners will be significantly greater than in the general population and the extent to which artificial tanning made a contribution.

Molecular Changes in UVR-Exposed Skin

The time-dependent gross physiologic changes described above are accompanied by more subtle molecular changes, invisible to the eye, that are the initiating events for the long-term detrimental effects of solar exposure. For example, in physiologically normal skin, clonal subpopulations of cells can be found that harbor p53 mutations (*45*). These occur much less frequently in sun-shielded skin. In sun-exposed skin these kinds of populations are not only more frequent but also larger in size. These p53-harboring cells appearing in normal skin are derived from earlier exposures to UVR, perhaps and most likely dating as far back as childhood. Every UVR exposure from the earliest years of childhood has the potential to induce new DNA photoproducts and their concomitant downstream effects. Human skin, to varying degrees depending on genetic makeup and general health status, possesses the capacity to repair these photoproducts. However, some may be unrepaired or misrepaired and hence lead to mutations. In individuals with genetically compromised DNA repair capacity (xeroderma pigmentosum patients), the lack of efficient repair leads to numerous skin cancers early in life (second decade) (*46*). Multiple skin cancers also occur in transplant patients who receive systemic immune-suppressive agents (*47,48*). Although there appears to be some controversy about the etiologic origin of these skin cancers, a recent analysis of p53 mutations in SCC from renal transplant recipients strongly implicates a role for prior UVR exposure (*49*).

p53 Induction and Mutations in Physiologically Normal Skin and Skin Cancers

The morphology of "sunburn" cells was originally described by Daniels et al. (*50*). Eventually it was shown that these were photodamaged cells in the process of undergoing apoptotic cell death. Apoptosis in skin cells exposed to UVR has also been correlated with the induction of p53. Because of its role in growth arrest and tumor suppression, p53 has been investigated as a surrogate marker in skin for the deleterious effects of UVR exposure. Pontén et al., for example, have shown that sunscreen application attenuated the induction of p53 after UVR exposure (*51*).

Using an allele-specific assay, Ananthaswamy et al. have demonstrated the ability of sunscreens to prevent some UVR-specific mutations in murine skin. In first of these studies a UVB source was employed, and hence the ability of a potent UVB sunscreen to reduce the frequency of mutations was not surprising (*52*). In a follow-up study similar findings were reported when a solar simulator was employed (*53*). Yet even further studies will be required to determine if mutations derived from indirect photosensitized reactions caused by long wavelength UVR photons (and possibly short wavelength visible light, neither of which is present in most solar-simulating light sources) are also prevented. As mentioned above, LeVee et al. (*14*) showed that solar simulators are typically devoid of longer UVA wavelengths.

Immune Suppression

Cells containing DNA damage that escapes faithful repair can be kept from proliferating by the skin immune system (*54*). However, exposure of skin to immune-suppressive agents (as in cardiac and renal transplant recipients) can lead to the development of large numbers of skin cancers. Sun exposure also suppresses skin immune surveillance. Once again, a detailed action spectrum for this immune suppression in human skin is not known. However, it has been repeatedly demonstrated that no sunscreen protects skin immune function as well as it protects skin from erythema (*55*). One recent paper made claim that some sunscreens protected the immune system to an extent that exceeded their label SPFs (*56*). However, a careful review revealed a flaw in the data analysis. The corrected analysis showed that the best of the sunscreens could only provide approximately 50% of their SPF values for immune protection (*57*). Thus, it can be safely assumed that a portion of the action spectrum for solar immune suppression lies beyond the UVB region and in the UVA region (*58*). How far into the UVA spectrum skin needs to be protected to prevent immune suppression is unknown at this time.

The critical role of immune suppression in skin cancer is buttressed by at least two observations. First, as described above, it is common for actinic keratosis to spontaneously regress, which suggests the involvement of an immune-mediated mechanism (*59*). Second, Colombo et al. have described the coexistence of regions of regression and progression in melanoma lesions (*60*). In addition, Wagner et al. have demonstrated that the immune response against human melanomas involves a distinct cytokine pattern (expression of granulocyte macrophage–colony-stimulating factor, IL-12, and IL-15) that is associated with spontaneous regression (*61*). When these results are considered with those of Wolf et al., who showed that UVB-type sunscreens do not prevent the progression of transplanted melanomas, the importance of broad spectrum UV protection is emphasized (*62*). These kinds of data raise the question of whether partial protection of the skin immune system by current sunscreen products is at least minimally adequate. In addition, once again they strongly suggest different wavelengths are responsible for different effects in skin (e.g., sunburn vs skin cancer vs immune suppression).

Elmets et al. have shown a close correlation between the action spectra for photoproduct formation and the induction of immunologic unresponsiveness of murine skin to dinitrofluorobenzene after exposure to low-dose UVR (*63*). DeFabo and Noonan showed a partial correlation of UV-induced *cis-trans* isomerization of urocanic acid with immune suppression (*64*).

Immune suppression has been shown to be related directly to DNA photoproduct formation. Studies in which immune suppression was assessed after the photoreversal or enzymatic removal of pyrimidine dimers showed a partial restoration of immune function (*65*). However, an action spectrum for this effect has not been reported. Whether these effects are limited to the formation of pyrimidine dimers or whether the induction of base oxidation processes caused by longer UVA wavelengths could also lead to skin immune suppression is unknown. Further complicating the issue of action spectra, Kim et al. reported that the suppression of delayed and contact hypersensitivity responses demonstrated different UV dose responses, suggesting different underlying biologic mechanisms (*66*). Similar findings would be expected in human skin. These limited studies suggest that the multitude of immune events could have different action spectra so that selecting any one as a surrogate marker for the immune-protective assay of sunscreens could be short-sighted and potentially misleading (*67*).

Finally, these data suggest that immune toxic effects may play a stronger role than previously appreciated in the development of melanoma. It is widely appreciated that SCC is common in immune-suppressed transplant recipients; there are similar data for premalignant melanocytic lesions (*68*). These data make it even more urgent to determine immune-suppressive action spectra in human skin.

Although it is common to assume there is a relationship between skin cancers and sun exposure, it is important to note the different correlations for anatomic locations of different kinds of skin cancer. There is a strong correlation between sun exposure and SCC but a somewhat weaker association for BCC and MM (*69*). Analyses of SCC and BCC demonstrate the signature effect of UVR as characteristic p53 mutations (*70*). However, when MM are examined, the incidence of p53 mutation is lower, late arising, and not conclusively implicative of UVR exposure [see Zerp et al. (*71*) and references therein].

Table 1. FDA-approved sunscreen ingredients and maximum concentrations.[a]

Ingredient	Maximum concentration (%)
Aminobenzoic acid	15
Avobenzone	3
Cinoxate	3
Dioxybenzone	3
Homosalate	15
Menthyl anthranilate	5
Octocrylene	10
Octyl methoxycinnamate	7.5
Octyl salicylate	5
Oxybenzone	6
Padimate-O	8
Phenylbenzimidazole sulfonic acid	4
Sulisobenzone	10
Titanium dioxide	25
Trolamine salicylate	12
Zinc oxide	25

[a]Data from the Federal Register (*95*).

Action Spectrum for Photoelastosis

Actinic damage without skin cancer can result from occupational or recreational activities. The skin becomes wrinkled, leathery, and variously pigmented. If this aged skin is compared to unexposed buttock skin, differences in the organization of collagen and elastin can be readily observed (*72*). These may be a result of direct photochemical modifications of the proteins or perhaps posttranslational effects. Regarding an action spectrum for these effects, conflicting results have been published. Kligman and Sayre reported a photoelastosis action spectrum very similar to that for erythema (primarily UVB dependent) (*73*). However, other reports showed a much greater contribution in the UVA region [see Sayre and Kligman (*74*) and references therein]. These different results have been attributed to the different methods used to assess photoaging and possibly to stray light effects (*73*).

Sunscreens

Sunscreens have been developed and tested by the industry and approved by the U.S. Food and Drug Administration (FDA) on the basis of their ability to prevent erythema (see Table 1 for list of approved ingredients). Using the FDA-approved SPF number as a guideline, a consumer can select a product to comfortably extend the time spent exposed to solar radiation without the risk of developing a sunburn. Although sunscreens are not recommended for this purpose, for all practical purposes their application ensures that the user is likely to spend more time in the sun than if the product were not employed. If the same wavelengths responsible for sunburn also caused the other deleterious effects in skin, this would not present a problem. However, as cited above, evidence is mounting to implicate contributions from other portions of the solar spectrum in skin cancer and photoaging. Hence there has been a significant effort to develop broader spectrum protection by adding UV-absorbing chemicals with UVA absorbency to sunscreens.

The high level of familiarity and public acceptance of SPF labeling are indicative of the success of an education campaign that began in the 1980s. Although some advocate a simplistic message about informative labeling of sunscreen products and public education messages about sun exposure and skin cancer, the success of the SPF program should encourage the development of a factual approach to development of a comprehensive public health message for sun safety. Thus, as opposed to a "dumbing down" approach, consumers should be presented with a scientifically accurate information package. The danger of dumbing down is indicated by a recent report. McCarthy et al. surveyed beachgoers in Galveston, Texas, and found that those who employed higher SPF sunscreens had a greater incidence of sunburn and spent more time in the sun (*75*). In addition it is time to recognize that some individuals may tolerate much more sun than others (*76*). This tolerance may be based on genetic makeup or tolerance developed over years of solar exposure. It is doubtful that an era can be rationally anticipated when people will not want to participate in outdoor activities despite the scare tactics currently in vogue (*77*).

Sunless Tanning

There has been some modest success in developing agents that cause skin pigmentation without the need for UVR exposure. Among these, dihydroxyacetone (DHA) has been available for many years (*78*). Although darkening of skin color is produced by DHA, it offers little protection to the underlying cells; hence excessive solar exposure must be avoided. Chemicals that can stimulate tyrosinase, an important intermediary of melanin synthesis, have also been incorporated in some topical products. These different agents, L-dopa (*79*), dinucleotides (*80*), and diols (*81*), may interact with different pathways of the melanogenesis system. For all of these products there are some issues that remain to be addressed. At this time it is not clear whether any long-term effects will arise, either with product use alone or combined with UVR exposure. Other issues are the levels of sun protection and the extent of this protection. The foregoing questions also apply to soluble synthetic forms of melanin that can be applied topically (*82*).

Another side of the melanin question has been addressed recently. Moan et al. have presented a novel hypothesis for melanoma induction (*83*). Specifically, it was suggested that melanin could act simultaneously as a photoprotective agent as well as an intermediary in photocarcinogenesis. The effect derived from the absorption of UVR by melanin would be related to its physiologic location. Melanin in the upper layers of skin would be photoprotective, but melanin in melanocytes could be photocarcinogenic. For direct experimental evidence for melanin-mediated damage, see Marrot et al. (*84*). The preceding two papers address one side of the question presented by Wood et al. (*85*) ("What's the use of generating melanin?"). In support of their hypothesis, Moan et al. cite statistics for

the induction of SCC, BCC, and MM in different countries at various latitudes (*86*).

Beneficial Effects of UVR Exposure

Exposure of skin cells to UVR is essential for the production of vitamin D (*87*). However, the necessary amounts of UVR needed are quite small and can be obtained by the exposure of hands and face to a few minutes of sunlight even in winter. In contrast, some have claimed that the use of sunscreens may unnecessarily suppress the production of vitamin D and lead to development of internal malignancies like colon and breast cancers (*88*). Others have reported that the general sense of well-being after sun exposure can be attributed to the induction of endorphins (*89*).

Epidemiologic Considerations

Epidemiology studies can relate human diseases to their causes. Excessive sun exposure, light complexion, and proximity to the equator have all been conclusively associated with an increased risk of skin cancer (*90*). The epidemiologic picture for the relationship between sunscreen use and skin cancer development is much less clear. As counterintuitive as this may appear, several studies have demonstrated a correlation of skin cancer with sunscreen use (*91*). Attempts to attribute these findings to weak sunscreens or improper use of potent sunscreens may be missing the mark. For the most part sunscreens have been and continue to be selective filters of solar UVR. Historically most have been very good UVB absorbers, hence their efficacy for the prevention of sunburn and possibly actinic keratosis and SCC. However, a sunscreen that filters UVB efficiently may permit the underlying cells to be exposed to greater amounts of the UVA portion of the solar spectrum. Sunscreen users are warned about using these products to extend their time in the sun. However, without a sunscreen or a somewhat protective tan, the average Caucasian would not be able to tolerate much more than approximately 10–20 min in the summer noonday sun without accumulating sufficient damage that would eventually lead to mild erythema. With proper application of an SPF-15 sunscreen, protected skin would not experience any erythema for several hours, yet would be exposed to all of the UVR wavelengths not absorbed by the sunscreen (*92*). Furthermore, the physiologic changes that occur during UVA erythema are not the same as those caused by sunburn (*93,94*).

Sunscreen Substantivity—Durability and Photostability Issues

For years substantivity has been used to refer to the ability of a sunscreen to resist washing off during swimming or sweating off during vigorous exercise. The recently released final FDA monograph (*95*) on sunscreen revised these definitions (Table 2). More recently, photosubstantivity issues have been raised, primarily regarding avobenzone. Sayre and Dowdy used an *in vitro* testing method to show that the exposure of avobenzone to physiologic doses of UVA led to its photodegradation (*96*). These studies are novel for two reasons. First, the authors did not assume that the only photochemistry would occur as a result of irradiation at the maximal wavelength of absorption. Second, they employed a modified solar simulator that more accurately reflects the UVA component of sunlight UVR. Solar simulators typically lack the longer wavelength region of the UVA sunlight spectrum. The UVA doses to which avobenzone was exposed ranged from 1 to 10 MEDs. In studies using actual sunscreen products, it was also shown that the UVA-induced photodegradation of avobenzone could also lead to the decomposition of normally stable UVB screening agents such as octylmethoxycinnamate and padimate-O. Recently it has been shown that the photodegradation of avobenzone could be prevented by formulating products with avobenzone and octocrylene (advertisement for Umbrelle). The triplet-state energies of these two molecules lie close enough to allow the transfer from avobenzone to octocrylene, thereby leading to avobenzone photostability. Yet these studies highlight the need to evaluate photochemistry, not only in sunscreen candidate molecules but also in the actual products as they would be formulated for sale to consumers.

Critical UVA Issues

Although sunscreens are highly efficacious for their ability to block the UVB portion of the solar spectrum, a critical issue that remains unresolved is their ability to screen UVA. The problem regarding UVA is 2-fold. First, detailed action spectra for biologic effects in human skin extending through the UVA do not exist. Second, there is no mandated regulation detailing how to test a product for UVA efficacy. Clearly these two issues are intertwined. The lack of data for the above can explain the omission of any directives on UVA in the recently issued final FDA monograph (*97*).

UVA Protection in Current Products

Rosenstein et al. have compared *in vitro* transmission spectra with SPF label specifications for 11 sunscreen products (*98*). Six of these products had labels claiming UVA protection. Spectrophotometric data for each product were convoluted with the International Commission on Illumination erythema action spectrum and the sunlight spectrum determined for solar noon, thereby producing effectiveness spectra for each product. Products claiming UVA protection had effectiveness levels ranging from 6 to 52% (measured from 320 to 400 nm). Especially noteworthy findings in this study are *a*) the different products varied widely; *b*) a product containing only TiO_2 claiming an SPF factor of 17 with no UVA claim provided the greatest degree of UVA screening, whereas another product with a prominent claim for UVA protection screened less than half of UVA wavelengths; *c*) two products with excellent UVA screening properties contained one of two strong UVA absorbers—parsol 1789 and mexoryl SX. The latter is not available in the United States, and the former has been the subject of some discussion regarding its photostability.

Table 2. Summary of FDA sunscreen regulations and terminology.[a]

- The FDA has established 30 as an upper limit for SPF labeling. Products with SPF values over 30 may be labeled as "30 plus" or "30+"[b]
- The SPF value for a product labeled "water resistant" or "very water resistant" will be the SPF determined in the water resistance test
- Extended wear claims concerning a specific number of hours of protection and the use of terms such as "all day protection" are not permitted
- Permissible labeling is limited to prevention of sunburn

SPF, sun protection factor. [a]See Federal Register (*95*). [b]Note added in proof: an industry petition has resulted in an extension of this deadline to 21 May 2001.

How Far into UVA?

This question cannot be answered with any degree of certainty until more action spectra studies are performed. Preliminary studies employing mice may be appropriate, but it is important to recognize that murine and human skin differ significantly in their cellular composition, structure, and responses to UVR (*99*). Action spectra studies should examine UVA-induced molecular effects in human skin. For example, *in vitro* studies show that the action spectrum for the induction of 8-hydroxyguanine extends into the visible region of the spectrum (*100*). The effects of UVA wavelengths on cytokine profiles should be performed. Because of the deeper penetration of UVA radiation (inverse relationship with wavelength), larger numbers of viable cells may potentially be affected.

Evaluation of UVA Protection

Two kinds of measurements have been suggested to characterize the UVA protective ability of sunscreens. In principle, as with UVB, erythema development could be employed. However, this is not a practical test when the times required to deliver the necessary UVA doses with and without sunscreen protection are considered. Two

different pigmentation effects, immediate and delayed, have also been suggested as measures of skin exposure to UVA in humans. Each has distinct advantages and disadvantages.

The advantage of IPD is that it occurs relatively early after UVA exposure. However, there is significant interindividual variability, which detracts from its routine use, and its action spectrum peaks at shorter wavelengths of the UVA region. Additonally, IPD is not photoprotective and hence serves no physiologic function (*101*).

Delayed pigmentation occurs over a much longer time frame but is more predictable, and might be preferred if the lag time were not so long. At this time there is no practical biologic end point known to act as a surrogate for photocarcinogenesis or photoaging. With additional action spectrum studies in the UVA region, a molecular marker for UVA exposure might be developed.

It has also been proposed that the well-characterized ability of 8-methoxypsoralen to sensitize skin to UVA be employed to test candidate products for their UVA screening ability (photosensitization protection factor) (*102*). However, it is unlikely that the psoralen action spectrum in skin will match all (if any) of the UVA-induced effects in nonsensitized human skin.

Considering the current need for broad spectrum UVB/UVA sunscreen products and the absence of a meaningful and clinically viable biologic marker, it would seem best to characterize that the sunscreen attenuates radiation in the spectral region thought to be harmful to skin cells. An *in vitro* instrumental method that characterizes the UVA screening ability of a sunscreen product has been described (*103*). A problem with this approach is the infinite variety of spectral shapes and the inability to easily compare products with different absorption spectra. A solution to the problem has been proposed by Diffey (*104*). By arbitrarily selecting the wavelength at which 10% of a sunscreen product absorbance falls, the so-called critical wavelength (CW) is defined. The term critical has met with some criticism. Perhaps a better description would be spectral screening factor and/or long wave index (LWI). The proponents of the CW method stress its simplicity, reproducibility, and ability to account for photosubstantivity issues. On the other hand, critics cite its lack of human relevance because it is an *in vitro* test where no biologic end point is measured. Although some have questioned the biologic relevance of CW analyses (i.e., no animal or human test subject), this concern may be a red herring. An ideal sunscreen product should function as a pure screening agent. Hence a method that analyzes its raw screening ability may be the most appropriate method. To avoid the judgmental tone of CW, here it is proposed that this index be renamed the LWI. Thus, the greater the LWI (Table 3), the further into the UVA spectrum a product's screening potential would extend. By comparing the LWI for different sunscreens, the consumer could assess the extent of potential protection offered by different products. The LWI is based on an instrumental method, which avoids any complications from idiosyncratic biologic variations from individual to individual. This technique is also reproducible and fast. In addition, the products can be pre-exposed to solar radiation to detect changes in LWI caused by photochemical degradation or instability (*105*). Because there is no need for human volunteers, it would be relatively inexpensive. Finally, using the LWI would eliminate the need to select from the wide range of skin biologic processes that may be affected by exposure to UVR. Considering the potentially different action spectra, this would solve the major quandary of which of these should be selected as the index for determining UVA protection.

Practical Aspects of Sunscreens

Sunscreens should be user friendly, with easy-to-understand directions about their proper and efficacious use. In mid-1999 no sunscreen product provided exact instructions on the amount of product to be applied to skin. This is important because studies have shown that much less than the effective SPF amount is typically applied by the user (*106,107*). The reason for underapplication of sunscreens is clear. Although the FDA-approved testing method requires the application of 2 mg/cm^2 to obtain the SPF claimed, nowhere on any sunscreen product are users advised the quantity of sunscreen that should be applied to protect their skin. Statements such as "apply liberally and frequently" give no guidance. For the average adult applying sunscreen, a quarter of a 4-oz bottle should be used. Perhaps bottles could come with a viewable "contents remaining" window gauge to assist the consumer. These studies also show that SPF does not fall off linearly with the amount applied but rather approaches the square. Hence, applying half the recommended amount of an SPF product would reduce the efficacy not by approximately 2-fold but by something closer to approximately 4-fold. The FDA-mandated SPF determination requires product application on the skin at a density of 2 mg/cm^2. The typical adult has nearly 2 m^2 of skin. This application rate translates into 40,000 mg or 40 g of product. Thus, total coverage of an adult at the beach would require more than an ounce of product or a quarter of a 4-oz bottle for a single application. If the person bathed in an ocean or pool, re-application would consume another ounce. Furthermore, for the typical family of four on a beach vacation, a single bottle would be a day's supply. If the vacation were for a week or so, to be adequately protected during their vacation they would need to purchase a 6-pack of sunscreen products.

Table 3. Long-wave index—definition and examples.[a]

Wavelength range (nm)	LWI rating[b]	Example[c]
< 320	0	*para*-Aminobenzoic acid
321–340	1	Octylmethoxycinnanmate
341–360	2	Octocrylene
361–380	3	None in monograph—TiO_2?
381–400	4	Avobenzone, ZnO
> 400	5	None in monograph

[a]According to Diffey (*104*), the sunscreen absorbance spectrum is reduced to a single index by determining the wavelength where the area under the spectrum from 290 to λ_{LWI} is 90% of the total. Here a 0–5 point scale is proposed to classify the products (see Figure 1 for an example). [b]To account for idiosyncratic physiologic effects, reflectance spectrophotometry could be used to determine LWI after sunscreens have been applied to human skin (*112*). Using this system would add a second rating to the sunscreen label. The primary number should remain the SPF value, which could appear in bold. The LWI would appear in parentheses or as a subscript. Alternatively, LWI could be given in Roman numerals. Possible examples: 30 (3), 30_3, 30-III. An informative label would explain this new labeling system and would also emphasize that the LWI is not a substitute for SPF. [c]LWI is meant to rate formulated sunscreen products, not individual ingredients. These examples are cited to illustrate the possible variations among the FDA-approved ingredients.

Progressive Warning Label

Currently sunscreen products may contain a label stating that the frequent use of the product may prevent sun damage such as photoaging and skin cancer (*108*). Yet these statements were promulgated in an era when much less was known about all of the effects of sunlight on skin biology. Given our new appreciation of the complex nature of skin cancer, the involvement of immune suppression, and the role of longer wavelengths of solar radiation in these processes, it would seem that such statements need to modified

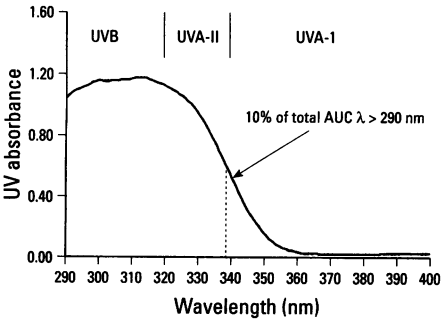

Figure 1. Long-wave index for a typical sunscreen. The UV spectrum is recorded from 290 nm (the shortest wavelength of UV radiation to which human skin is exposed). The point that demarcates 10% of the area under the absorption spectrum is used to define the long-wave index (arrow; see also Table 3).

drastically. In fact, all a label can say with any confidence is that the use of this product will prevent sunburn if used appropriately. One product that is commercially available contains the following statement: ". . .with sunscreen protection, UV exposure can still lead to skin cancer and premature aging, even if you don't burn." (*109*).

Tomorrow's Sunscreens

More research in skin photobiology will lead to better sunscreen products. It also appears that educational campaigns to make individuals aware of skin cancer-inducing practices and safe sun exposure practices and protection methods are having an impact on skin cancer incidence and detection. In the future, sunscreen product labels need to provide the consumer with more information, ranging from clear factual statements about the amount that needs to be applied to what sunscreens can and cannot do. As labeled now, most sunscreens products are confusing to the average user. Statements such as "apply liberally and frequently" are too vague to be informative. Others such as "do not use to extend time spent in the sun" are counterintuitive. Finally, the meaning of the acronym SPF should be changed from sun protection factor to sunburn protection factor to avoid giving the consumer an impression of solar invincibility and a false sense of security. SPF defined as sun protection factor connotes an impervious armor protecting against all assaults on skin biology. There likely never is to be any such product.

Adequate UVA protection and an appropriate testing method of UVA efficacy are the most pressing unmet needs. Although some *in vivo* biologic method would appear desirable, at present there is scarce biologic data for such an assessment. *In vitro* testing of sunscreens to determine the LWI can provide additional independent information relevant to the UVR screening contribution of sunscreen formulations in the UVA region.

A last crucial factor beyond the scope of this review concerns behavior modification. The consumer needs to appreciate the potentially detrimental consequences of sunbathing and tanning parlor usage. In summary we see that sunscreens are efficacious for the prevention of sunburn—the reason for which they have been designed and implemented. Although some have promoted daily use for the prevention of premature aging of the skin and the prevention of skin cancer, actual data are lacking to support these recommendations. Furthermore, the widespread implementation of such a recommendation could lead to increased chronic exposure to solar wavelengths not filtered by the sunscreens. Without shorter wavelengths to serve either as a early signal for induced photodamage or perhaps as a triggering event for skin adaptation, other events less likely to occur in full-spectrum solar-exposed skin could take place (*110*). The status of sun protection programs was reviewed by Geller (*111*). Factors involved in sunscreen use (peer attitudes, level of education, etc.) were discussed, as well as venues for the dissemination of sun protection information.

References and Notes

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